

Figure 1 : Alignment of N-terminal fragments of Human Hedgehog Proteins

1

| | | | | | |
|--------|------------|------------|------------|------------|------------|
| Indian | CGPGRVVGSR | RRPPRK-LVP | LAYKQFSPNV | PEKTLGASGR | YEGKIARSSE |
| Sonic | CGPGRGFG-K | RRHPKK-LTP | LAYKQFIPNV | AEKTLGASGR | YEGKISRNE |
| Desert | CGPGRGPVGR | RRYARKQLVP | LLYKQFVPGV | PERTLGASGP | AEGRVARGSE |

51

| | | | | | |
|--------|------------|------------|------------|------------|------------|
| Indian | RFKELTPNYN | PDIIFKDEEN | TGADRLMTQR | CKDRLNSLAI | SVMNQWPGVK |
| Sonic | RFKELTPNYN | PDIIFKDEEN | TGADRLMTQR | CKDKLNALAI | SVMNQWPGVK |
| Desert | RFRDLVPNYN | PDIIFKDEEN | SGADRLMTER | CKERVNALAI | AVNMNWPGVR |

101

| | | | | | |
|--------|------------|------------|------------|------------|------------|
| Indian | LRVTEGWDED | GHHSEESLHY | EGRAVDITTS | DRDRNKYGLL | ARLAVEAGFD |
| Sonic | LRVTEGWDED | GHHSEESLHY | EGRAVDITTS | DRDRSKYGLM | ARLAVEAGFD |
| Desert | LRVTEGWDED | GHHAQDSLHY | EGRALDITTS | DRDRNKYGLL | ARLAVEAGFD |

151

| | | | | |
|--------|------------|------------|--------|---------------|
| Indian | WVYYESKAHV | HCSVKSEHSA | AAKTGG | SEQ ID NO: 23 |
| Sonic | WVYYESKAHI | HCSVKAENSV | AAKSGG | SEQ ID NO. 24 |
| Desert | WVYYESRNHV | HVSVKADNSL | AVRAGG | SEQ ID NO. 25 |

Gap(s), indicated by -, added to facilitate alignment

Figure 2: SEQ ID NO: 26 is the consensus sequence of a hedgehog protein suitable for use in developing the conjugated proteins of the invention, antagonist, where "Xaa" indicates amino acids that differ between the Sonic, Indian and Desert hedgehog proteins.

C* G P G R Xaa1 Xaa2 Xaa3 Xaa4 Xaa5 R R Xaa6 Xaa7 Xaa8 K Xaa9 L Xaa10 P
L Xaa11 Y K Q F Xaa12 P Xaa13 V Xaa14 E K T L G A S G R
Xaa15 E G K Xaa16 Xaa17 R Xaa18 S E R F K Xaa19 L Xaa20 P N Y N
P D I I F K D E E N Xaa21 G A D R L M T Xaa22 R
C K Xaa23 Xaa24 Xaa25 N S L A I Xaa26 V M N Xaa27 W P G V K
L R V T E G W D E D G H H X2aa8 Xaa29 Xaa30 S L H Y
E G R A V D I T T S D R D R Xaa31 K Y G Xaa32 L
A R L A V E A G F D W V Y Y E S Xaa33 Xaa34 H Xaa35
H Xaa36 S V K Xaa37 Xaa38 Xaa39 S Xaa40 A A Xaa41 Xaa42 G G

Where

C* is a cysteine that may be modified, altered or substituted within another moiety or series of moieties as described herein;

| | | |
|----------------------------|----------------------------|-----------------------------|
| Xaa1 is either V or G; | Xaa2 is either V, E or P | Xaa3 is either G or V |
| Xaa4 is either S or G; | Xaa5 is either R or K; | Xaa6 is either P, H or Y; |
| Xaa7 is either P or A; | Xaa8 is either R or K; | Xaa9 is any amino acid; |
| Xaa10 is either V or T; | Xaa11 is either A or L; | Xaa14 is either P or A; |
| Xaa12 is either S, I or V; | Xaa13 is either N or G; | Xaa17 is either A or S; |
| Xaa15 is either Y or A; | Xaa16 is either I or V; | Xaa20 is either T or V; |
| Xaa18 is either S, N or G; | Xaa19 is either E or D; | Xaa23 is either D or E; |
| Xaa21 is either T or S; | Xaa22 is either Q or E; | Xaa26 is either S or A; |
| Xaa24 is either R or K; | Xaa25 is either L or V; | Xaa29 is either E or Q; |
| Xaa27 is either Q or M; | Xaa28 is either S or A; | Xaa32 is either L or M; |
| Xaa30 is either E or D; | Xaa31 is either N or S; | Xaa35 is either V or I; |
| Xaa33 is either K or R; | Xaa34 is either A or N; | Xaa38 is either E or D; |
| Xaa36 is either C or V; | Xaa37 is either S or A; | Xaa41 is either K or R; and |
| Xaa39 is either H or N; | Xaa40 is either A, V or L; | |
| Xaa42 is either T, S or A. | | |